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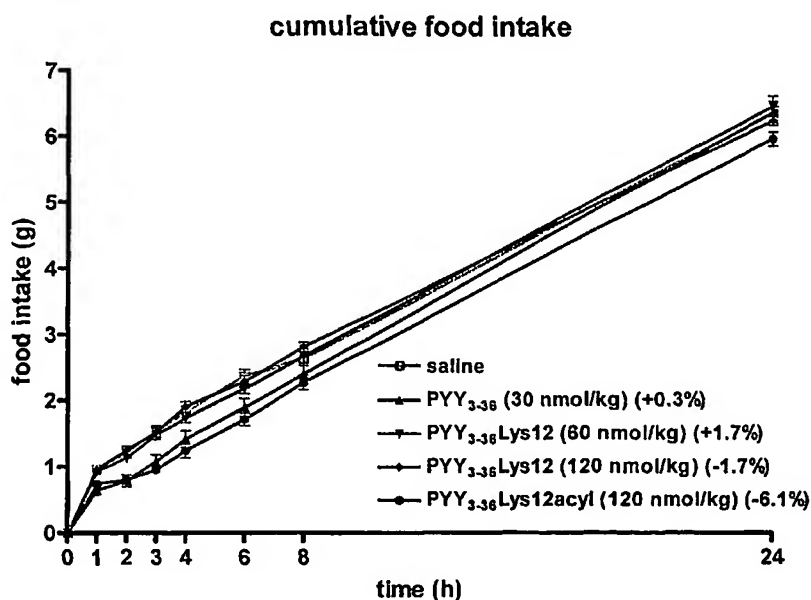
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(54) Title: NOVEL COMPOUNDS AND THEIR EFFECTS ON FEEDING BEHAVIOUR



(57) Abstract: The invention provides a compound of formula (I) : X- PYY* (3-36) (I) wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ue; PYY*(3-36) representing PYY (3-36) in which one or more residues is replaced by an acylated lysine group, the acyl group being selected from: CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl; a variant or derivative thereof; or a salt or solvate thereof. The compounds are effective in inducing satiety and suppressing appetite and they are thus useful in treating various diseases, including obesity.

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NOVEL COMPOUNDS AND THEIR EFFECTS ON FEEDING BEHAVIOUR

1. FIELD OF THE INVENTION

5 This application relates to the use of agents to control appetite, feeding, food intake, energy expenditure and calorie intake, particularly in the field of obesity.

2. BACKGROUND OF THE INVENTION

10 According to the National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994), between one third and one half of men and women in the United States are overweight. In the United States, sixty percent of men and fifty-one percent of women, of the age of 20 or older, are either overweight or obese. In addition, a large percentage of children in the United States are overweight or obese.

15 The cause of obesity is complex and multi-factorial. Increasing evidence suggests that obesity is not a simple problem of self-control but is a complex disorder involving appetite regulation and energy metabolism. In addition, obesity is associated with a variety of conditions associated with increased morbidity and mortality in a population. Although the etiology of obesity is not definitively established, genetic, metabolic, biochemical,
20 cultural and psychosocial factors are believed to contribute. In general, obesity has been described as a condition in which excess body fat puts an individual at a health risk.

There is strong evidence that obesity is associated with increased morbidity and mortality. Disease risk, such as cardiovascular disease risk and type 2 diabetes disease risk, increases
25 independently with increased body mass index (BMI). Indeed, this risk has been quantified as a five percent increase in the risk of cardiac disease for females, and a seven percent increase in the risk of cardiac disease for males, for each point of a BMI greater than 24.9 (see Kenchaiah et al., *N. Engl. J. Med.* 347:305, 2002; Massie, *N. Engl. J. Med.* 347:358, 2002). In addition, there is substantial evidence that weight loss in obese persons
30 reduces important disease risk factors. Even a small weight loss, such as 10% of the initial

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body weight in both overweight and obese adults has been associated with a decrease in risk factors such as hypertension, hyperlipidemia, and hyperglycemia.

Although diet and exercise provide a simple process to decrease weight gain, overweight and obese individuals often cannot sufficiently control these factors to effectively lose weight. Pharmacotherapy is available; several weight loss drugs have been approved by the Food and Drug Administration that can be used as part of a comprehensive weight loss program. However, many of these drugs have serious adverse side effects. When less invasive methods have failed, and the patient is at high risk for obesity related morbidity or mortality, weight loss surgery is an option in carefully selected patients with clinically severe obesity. However, these treatments are high-risk, and suitable for use in only a limited number of patients. It is not only obese subjects who wish to lose weight. People with weight within the recommended range, for example, in the upper part of the recommended range, may wish to reduce their weight, to bring it closer to the ideal weight. Thus, a need remains for agents that can be used to effect weight loss in overweight and obese subjects.

In WO03/026591, it is disclosed that peripheral administration of peptide YY (hereinafter PYY), or an agonist thereof, to a subject results in decreased food intake, caloric intake, and appetite, and an alteration in energy metabolism. It is disclosed that the PYY or agonist thereof is preferably an N-terminally deleted PYY molecule PYY₃₋₃₆.

3. SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I):

X- PYY* (3-36) (I)

Wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile; PYY*(3-36) representing PYY (3-36) in which one or more residues is replaced by an acylated lysine group, the acyl group being selected from: CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl; a variant or derivative thereof; or a salt or solvate thereof.

The present invention also provides a compound of formula (Ia):

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X-PYY* (3-36) (Ia)

PYY (3-36) being:

3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ile	Lys	Pro	Glu	Ala	Pro	Gly	Glu	Asp	Ala	Ser	Pro	Glu	Glu	Leu

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Asn	Arg	Tyr	Tyr	Ala	Ser	Leu	Arg	His	Tyr	Leu	Asn	Leu	Val	Thr

5

33	34	35	36
Arg	Gln	Arg	Tyr

SEQ ID NO:2

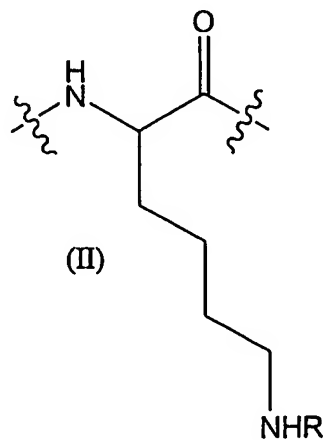
Wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile.

PYY*(3-36) representing PYY (3-36) in which one or more of residues:

3 - Ile	7 - Ala
9 - Gly	12 - Ala
17 - Leu	22 - Ala
24 - Leu	28 - Leu

10

is replaced by a residue (II):



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wherein R is selected from CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl;
a variant or derivative thereof; or a salt or solvate thereof.

- 5 The invention also provides uses of a compound of formula (I), methods that use a compound of formula (I), compositions comprising a compound of formula (I), and methods of making a compound of formula (I).

4. BRIEF DESCRIPTION OF THE FIGURES

- 10 **Figure 1** shows the results of an experiment in which the appetite suppressing effects in mice of a compound of the invention were compared with native PYY(3-36) (SEQ ID NO:2), a further analogue of PYY(3-36) and saline.
Figures 2 a) to 2 g) show the results of the experiment of **Figure 1** broken down by time interval.
- 15 **Figure 3** shows the results of the experiment of **Figure 1** expressed as a % of saline.
Figures 4 a) to 4 g) show the results of an experiment which the appetite suppressing effects in mice of a compound of the invention at various dosages were compared with native PYY(3-36) and saline.
Figure 5 shows the results of the experiment of **Figure 4** expressed as a % of saline.
- 20

5. SEQUENCE LISTING

The amino acid sequences listed in the application are shown using standard letter abbreviations for amino acids.

25 6. DEFINITIONS

In order to facilitate review of the various embodiments of this disclosure, the following explanations of specific terms are provided:

- Animal:** Living multi-cellular vertebrate organisms, a category that includes, for example,
30 mammals and birds. The term mammal includes both human and non-human mammals.
Similarly, the term "subject" includes both human and veterinary subjects.

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Appetite: A natural desire, or longing for food. In one embodiment, appetite is measured by a survey to assess the desire for food. Increased appetite generally leads to increased feeding behavior.

- 5 **Appetite Suppressants:** Compounds that decrease the desire for food. Commercially available appetite suppressants include, but are not limited to, amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine fenfluramine, dexfenfluramine, and fluoxetine.
- 10 **Body Mass Index (BMI):** A mathematical formula for measuring body mass, also sometimes called Quetelet's Index. BMI is calculated by dividing weight (in kg) by height² (in meters²). The current standards for both men and women accepted as "normal" are a BMI of 20-24.9 kg/m². In one embodiment, a BMI of greater than 25 kg/m² can be used to identify an obese subject. Grade I obesity corresponds to a BMI of 25-29.9 kg/m².
- 15 Grade II obesity corresponds to a BMI of 30-40 kg/m²; and Grade III obesity corresponds to a BMI greater than 40 kg/m² (Jequier, *Am. J Clin. Nutr.* 45:1035-47, 1987). Ideal body weight will vary among species and individuals based on height, body build, bone structure, and sex.
- 20 **Conservative substitutions:** The replacement of an amino acid residue by another, biologically similar residue in a polypeptide. The term "conservative variation" also includes the use of a substituted amino acid, i.e. an amino with one or more atoms replaced with another atom or group, in place of a parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.
- 25 **Diabetes:** A failure of cells to transport endogenous glucose across their membranes either because of an endogenous deficiency of insulin and/or a defect in insulin sensitivity. Diabetes is a chronic syndrome of impaired carbohydrate, protein, and fat metabolism owing to insufficient secretion of insulin or to target tissue insulin resistance. It occurs in
- 30 two major forms: insulin-dependent diabetes mellitus (IDDM, type I) and non-insulin dependent diabetes mellitus (NIDDM, type II) which differ in etiology, pathology, genetics, age of onset, and treatment.

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The two major forms of diabetes are both characterized by an inability to deliver insulin in an amount and with the precise timing that is needed for control of glucose homeostasis.

Diabetes type I, or insulin dependent diabetes mellitus (IDDM) is caused by the

5 destruction of β cells, which results in insufficient levels of endogenous insulin. Diabetes type II, or non-insulin dependent diabetes, results from a defect in both the body's sensitivity to insulin, and a relative deficiency in insulin production.

Food intake: The amount of food consumed by an individual. Food intake can be

10 measured by volume or by weight. For example, food intake may be the total amount of food consumed by an individual. Or, food intake may be the amount of proteins, fat, carbohydrates, cholesterol, vitamins, minerals, or any other food component, of the individual. "Protein intake" refers to the amount of protein consumed by an individual. Similarly, "fat intake," "carbohydrate intake," "cholesterol intake," "vitamin intake," and
15 "mineral intake" refer to the amount of proteins, fat, carbohydrates, cholesterol, vitamins, or minerals consumed by an individual.

Hyperpolarization: A decrease in the membrane potential of a cell. Inhibitory

neurotransmitters inhibit the transmission of nerve impulses via hyperpolarization. This
20 hyperpolarization is called an inhibitory postsynaptic potential (IPSP). Although the threshold voltage of the cell is unchanged, a hyperpolarized cell requires a stronger excitatory stimulus to reach threshold.

Normal Daily Diet: The average food intake for an individual of a given species. A

25 normal daily diet can be expressed in terms of caloric intake, protein intake, carbohydrate intake, and/or fat intake. A normal daily diet in humans generally comprises the following: about 2,000, about 2,400, or about 2,800 to significantly more calories. In addition, a normal daily diet in humans generally includes about 12 g to about 45 g of protein, about 120 g to about 610 g of carbohydrate, and about 11 g to about 90 g of fat. A
30 low calorie diet would be no more than about 85%, and preferably no more than about 70%, of the normal caloric intake of a human individual.

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In animals, the caloric and nutrient requirements vary depending on the species and size of the animal. For example, in cats, the total caloric intake per pound, as well as the percent distribution of protein, carbohydrate and fat varies with the age of the cat and the reproductive state. A general guideline for cats, however, is 40 cal/lb/day (18.2 cal/kg/day). About 30% to about 40% should be protein, about 7% to about 10% should be from carbohydrate, and about 50% to about 62.5% should be derived from fat intake. One of skill in the art can readily identify the normal daily diet of an individual of any species.

- 10 **Obesity:** A condition in which excess body fat may put a person at health risk (see Barlow and Dietz, *Pediatrics* 102:E29, 1998; National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI), *Obes. Res.* 6 (suppl. 2):51S-209S, 1998). Excess body fat is a result of an imbalance of energy intake and energy expenditure. For example, the Body Mass Index (BMI) may be used to assess obesity. In one commonly used
- 15 convention, a BMI of 25.0 kg/m² to 29.9 kg/m² is overweight, while a BMI of 30 kg/m² is obese.

- In another convention, waist circumference is used to assess obesity. In this convention, in men a waist circumference of 102 cm or more is considered obese, while in women a waist
- 20 circumference of 89 cm or more is considered obese. Strong evidence shows that obesity affects both the morbidity and mortality of individuals. For example, an obese individual is at increased risk for heart disease, non-insulin dependent (type 2) diabetes, hypertension, stroke, cancer (e.g. endometrial, breast, prostate, and colon cancer), dyslipidemia, gall bladder disease, sleep apnea, reduced fertility, and osteoarthritis, amongst others (see
- 25 Lyznicki et al., *Am. Fam. Phys.* 63:2185, 2001).

- Overweight:** An individual who weighs more than their ideal body weight. An overweight individual can be obese, but is not necessarily obese. For example, an overweight individual is any individual who desires to decrease their weight. In one
- 30 convention, an overweight individual is an individual with a BMI of 25.0 kg/m² to 29.9 kg/m²

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Pegylated and pegylation: the process of reacting a poly(alkylene glycol), preferably an activated poly(alkylene glycol) to form a covalent bond. A facilitator may be used, for example an amino acid, e.g. lysine. Although "pegylation" is often carried out using poly(ethylene glycol) or derivatives thereof, such as methoxy poly(ethylene glycol), the
5 term is not limited herein to the use of methoxy poly(ethylene glycol) but also includes the use of any other useful poly(alkylene glycol), for example poly(propylene glycol).

Peptide YY (PYY): The term PYY as used herein refers to a peptide YY polypeptide, a hormone secreted into the blood by cells lining the lower small intestine (the ileum) and
10 the colon.

Peripheral Administration: Administration outside of the central nervous system. Peripheral administration does not include direct administration to the brain. Peripheral administration includes, but is not limited to intravascular, intramuscular, subcutaneous,
15 inhalation, oral, rectal, transdermal or intra-nasal administration

Polypeptide: A polymer in which the monomers are amino acid residues which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-isomers being preferred. The
20 terms "polypeptide" or "protein" as used herein encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "polypeptide" is specifically covers naturally occurring proteins, as well as those which are recombinantly or synthetically produced. The term "polypeptide fragment" refers to a portion of a polypeptide, for example a fragment which exhibits at least one useful sequence in binding
25 a receptor. The term "functional fragments of a polypeptide" refers to all fragments of a polypeptide that retain an activity of the polypeptide. Biologically functional peptides can also include fusion proteins, in which the peptide of interest has been fused to another peptide that does not decrease its desired activity.

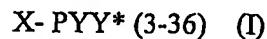
Therapeutically effective amount: A dose sufficient to prevent advancement, or to cause regression of a disorder, or which is capable of relieving a sign or symptom of a disorder, or which is capable of achieving a desired result. In several embodiments, a
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therapeutically effective amount of a compound of the invention is an amount sufficient to inhibit or halt weight gain, or an amount sufficient to decrease appetite, or an amount sufficient to reduce caloric intake or food intake or increase energy expenditure.

5 7. DETAILED DESCRIPTION

As mentioned above, the invention provides a compound of formula (I):



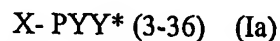
wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile;

PYY*(3-36) representing PYY (3-36) (SEQ ID NO:2) in which one or more residues is
 10 replaced by an acylated lysine group, the acyl group being selected from: CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl; a variant or derivative thereof; or a salt or solvate thereof.

In particular, the residue or residues that are replaced are selected from the neutral, non-
 15 cyclic residues. Preferably, the residue or residues that are replaced are selected from the neutral, non-cyclic residues and are not proline residues. Preferred residues to be substituted include Alanine, Leucine, Isoleucine and Glycine, in particular Alanine. Preferably, one, two or three residues are replaced by an acylated lysine group. Preferably, the replacement of the residue concerned does not significantly reduce the affinity of the
 20 PYY (3-36) molecule at the Y2 receptor. Binding at the Y2 receptor can be measured by standard methods.

In particular, the invention provides a compound of formula (Ia):

25



Wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile.

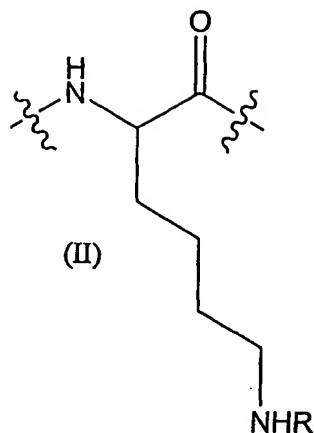
PYY*(3-36) representing PYY (3-36) (SEQ ID NO:2) in which one or more of residues:

3 - Ile	7 - Ala
9 - Gly	12 - Ala

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17 - Leu	22 - Ala
24 - Leu	28 - Leu

is replaced by a residue (II):



- 5 wherein R is selected from CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl;
a variant or derivative thereof; or a salt or solvate thereof.

10 The compounds of the invention as represented in formula (I) and (Ia) are related to PYY₃₋₃₆ and they have acyl side chains attached in a specific manner at particular locations in the molecule. Typically, the acyl groups are of the form R₁CO-, where R₁ can be a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₅₋₁₀ aryl group or a C₅₋₁₀ ar-C₁₋₂₀ alkyl group. Particular R₁ alkyl groups include lauroyl, stearyl and palmityl, and particular alkenyl groups include oleyl.

15

The effects of administration of 240 nmol/kg PYY₃₋₃₆ Lys₁₂lauroyl (PYY₃₋₃₆ with the residue at position 12 replaced with a lysine residue coupled to a lauroyl group, SEQ ID NO: 14) and 60 nmol/kg PYY₃₋₃₆ to mice were investigated and it was found that the administration of 240 nmol/kg PYY₃₋₃₆ Lys₁₂lauroyl resulted in a slower onset of food intake reduction than that seen with 60 nmol/kg of the native PYY₃₋₃₆ but that the administration of 240 nmol/kg PYY₃₋₃₆ Lys₁₂lauroyl showed greater persistence of effect when compared with the administration of 60 nmol/kg of native PYY₃₋₃₆.

20

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Increased duration of appetite suppression can be particularly important to avoid the effect known as "escape". A short duration appetite suppressant may reduce appetite for the time covered by one meal and, in that meal, the subject typically eats less food. If, however, the appetite suppressant is then metabolized or otherwise removed from the circulation of the subject, then by the time of the next mealtime, the subject can regain its "normal" appetite. In view of the subject having eaten a small meal at the previous mealtime, the subject may in fact have an increased appetite by the time of the second meal. If the subject satisfies that appetite, it is possible for the food intake over the two meals, in total, to be no lower than the food intake would have been without the appetite suppressant. That is to say that the subject may have "escaped" from the effects of the appetite suppressant. "Escape" can be reduced by using additional doses of appetite suppressant, or by using an appetite suppressant with a longer duration of action. If the subject has a reduced appetite for longer, then the degree to which it can make up the missed food from one meal in the next meal is reduced as there is a practical limit to the total capacity for food in a particular meal.

Furthermore, it has been found that prolonged continuous infusion of a short duration appetite suppressant is less effective than administration of a single dose of a longer acting appetite suppressant even if the level of the shorter acting suppressant is maintained in the bloodstream for a similar length of time as the longer acting suppressant by continuous dosing.

Preferably, the PYY*₃₋₃₆ is based on human PYY₃₋₃₆.

25

The human full length PYY polypeptide is shown in SEQ ID NO: 1; human PYY₃₋₃₆ is shown in SEQ ID NO: 2. The subscripts refer to the location on the full length PYY molecule in the species in question, beginning at the N-terminus. Thus PYY₃₋₃₆ is a peptide PYY molecule lacking amino acids 1 and 2 at the N-terminus. Analogous numbering is used for other fragments and variants of PYY described herein. Human PYY₃₋₃₆ is:

30

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3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ile	Lys	Pro	Glu	Ala	Pro	Gly	Glu	Asp	Ala	Ser	Pro	Glu	Glu	Leu

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Asn	Arg	Tyr	Tyr	Ala	Ser	Leu	Arg	His	Tyr	Leu	Asn	Leu	Val	Thr

33	34	35	36
Arg	Gln	Arg	Tyr

SEQ ID NO:2

Preferably, one, two or three residues are each replaced by a residue (II). One or two
 5 residues may each be replaced by a residue (II). For example, one residue is replaced by a residue (II).

In one embodiment of the invention, the residue or residues replaced are selected from 3 –
 10 Ile, 7 – Ala, 9 – Gly, 12 – Ala, 17 – Leu, 22 – Ala and 24 – Leu; more preferably from 3 – Ile, 7 – Ala, 9 – Gly, 12 – Ala, 17 – Leu and 22 – Ala; particularly from 3 – Ile, 7 – Ala, 9 – Gly, 12 – Ala and 17 – Leu, for example from 3 – Ile, 7 – Ala, 9 – Gly and 12 – Ala.

In another embodiment of the invention, the residues replaced are selected from 7 – Ala,
 15 12 – Ala, and 22 – Ala. More preferably, the residues replaced are selected from 7 – Ala, 12 – Ala, for example 12 – Ala.

In one particular embodiment, the molecule of formula (I) is X-PYY₃₋₃₆ Lys₁₂- Acyl, ie X-
 20 PYY₃₋₁₁ - (Lys- Acyl) - PYY₁₃₋₃₆. PYY₃₋₁₁ refers to a portion of the human PYY molecule containing residues 3 to 11 and PYY₁₃₋₃₆ refers to a portion of the human PYY molecule containing residues 13 to 36. The human PYY₃₋₁₁ and the human PYY₁₃₋₃₆ sequences are shown as SEQ ID NO:11 and SEQ ID NO:12 respectively (see Table 2). PYY₃₋₃₆ Lys₁₂ refers to a human PYY molecule which lacks amino acids 1 and 2 at the N terminus and
 25 where a lysine residue has been substituted for the Alanine at position 12. The sequence of

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PYY₃₋₃₆ Lys₁₂ is shown as SEQ ID NO:13 in Table 2. PYY₃₋₃₆ Lys₁₂ - Acyl refers to a human PYY molecule which lacks amino acids 1 and 2 at the N terminus and where a Lysine residue with an acylated side chain has been substituted for the Alanine at position 12. The sequence of PYY₃₋₃₆ Lys₁₂-Acyl is shown as SEQ ID NO:14 in Table 2. To reflect
 5 the fact that the Lysine side chain has been modified, the letter X is used to denote position 12 in PYY₃₋₃₆ Lys₁₂-Acyl.

The PYY₃₋₃₆ portions in a molecule of the invention may be, or may be related to, a PYY from a species other than human. The sequence of PYYs of various species are included
 10 in Table 1 (SEQ ID NOS: 3 to 10), including e.g. rat and pig PYY. The PYY₃₋₃₆ portions in a molecule of the invention may also be taken from any of those sequences.

Table 1: PYY sequence of various species

15	PEPTIDE YY	AA SEQUENCE
	Human	YPIKPEAPGEDASPEELNRYASLRHYLNLVTRQRY (SEQ ID NO: 1)
	Human 3-36	IKPEAPGEDASPEELNRYASLRHYLNLVTRQRY (SEQ ID NO: 2)
	Rat	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 3)
	Pig	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 4)
20	Guinea pig	YPSKPEAPGSDASPEELARYASLRHYLNLVTRQRY (SEQ ID NO: 5)
	Frog	YPPKPENPGEDASPEEMTKYLTALRHYNLVTRQRY (SEQ ID NO: 6)
	Raja	YPPKPENPGDDAAPEELAKYYALSRLHYNLITRQRY (SEQ ID NO: 7)
	Dogfish	YPPKPENPGEDAPPEELAKYYALSRLHYNLITRQRY (SEQ ID NO: 8)
	Lampetra	FPPKPDNPGDNASPEQMARYKAAVRHYNLITRQRY (SEQ ID NO: 9)
25	Petromyzon	MPPKPDNPSPDASPEELSKYMLAVRNYNLITRQRY (SEQ ID NO: 10)

Table 2: PYY sequences of the present invention, or discussed in the context of the present invention:

30	PYY ₃₋₁₁	IKPEAPGED (SEQ ID NO: 11)
	PYY ₁₃₋₃₆	SPEELNRYASLRHYLNLVTRQRY (SEQ ID NO: 12)
	PYY ₃₋₃₆ Lys ₁₂	IKPEAPGEDK _S PEELNRYASLRHYLNLVTRQRY (SEQ ID NO: 13)
	PYY ₃₋₃₆ ModLys ₁₂	IKPEAPGEDX _S PEELNRYASLRHYLNLVTRQRY (SEQ ID NO: 14)

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In a similar manner to native PYY and PYY₃₋₃₆, the compounds of the invention are typically selective for the Y2 receptor. That is, they bind with higher affinity to Y2 compared to other receptors, such as Y1, Y3, Y4, Y5 and Y6. These receptors are
5 recognized based on binding affinities, pharmacology, and sequence (if known). Most, if not all of these receptors are G protein coupled receptors. The Y1 receptor is generally considered to be postsynaptic and mediates many of the known actions of neuropeptide Y in the periphery. Originally, this receptor was described as having poor affinity for C-terminal fragments of neuropeptide Y, such as the 13-36 fragment, but interacts with the
10 full length neuropeptide Y and peptide YY with equal affinity (e.g., see PCT publication WO 93/09227).

Pharmacologically, the Y2 receptor is distinguished from Y1 by exhibiting affinity for C-terminal fragments of neuropeptide Y. The Y2 receptor is most often differentiated by the
15 affinity of neuropeptide Y(13-36), although the 3-36 fragment of neuropeptide Y and peptide YY provides improved affinity and selectivity (see Dumont et al., *Society for Neuroscience Abstracts* 19:726, 1993). Signal transmission through both the Y1 and the Y2 receptors are coupled to the inhibition of adenylate cyclase. Binding to the Y2 receptor was also found to reduce the intracellular levels of calcium in the synapse by selective
20 inhibition of N-type calcium channels. In addition, the Y2 receptor, like the Y1 receptors, exhibits differential coupling to second messengers (see U.S. Patent No. 6,355,478). Y2 receptors are found in a variety of brain regions, including the hippocampus, substantia nigra-lateralis, thalamus, hypothalamus, and brainstem. The human, murine, monkey and rat Y2 receptors have been cloned (e.g., see U.S. Patent No. 6,420,352 and U.S. Patent No.
25 6,355,478).

Binding to the Y2 receptor can be assessed by standard techniques. For example, an ELISA or fluorescence-based assay may be used to assess binding of a compound at the receptor. A cell-based functional assay can be used to assess whether a compound is an
30 agonist or an antagonist of the receptor.

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The mechanism by which the Acylated lysine side chain brings about its advantageous effects is not known. It is possible that its lipophilic nature causes the moiety to bind with albumin and thus brings about a reduced rate of clearance from a subject thus increasing half life and duration of effect.

5

Whilst the acyl side chains may be lower acyl, for example C₁- C₉ acyl, especially C₁₋₆ acyl, they are preferred to be C₄₋₄₀, in particular C₈₋₂₅ acyl, especially C₁₆ or C₁₈ acyl. Lauroyl is especially preferred as an acyl side chain as is palmityl. The acyl substituent is attached to the lysine residue in such a way that a carboxyl group of the acyl substituent

10 forms an amide bond with an amino group of the lysine residue.

Variants:

The PYY₃₋₃₆ portions of the molecule may be variants of the equivalent native portions, for example the PYY₃₋₃₆ portions may be variants of the equivalent native human portions. Variants include PYY₃₋₃₆ portions with deletions, insertions, inversions, repeats and substitutions, (e.g., conservative substitutions and non-conservative substitutions; see, e.g., Table 3 below) which retain at least some of the activity of a corresponding non-variant molecule when in a molecule of the invention. More than one amino acid (e.g., 2, 3 or 4)

15 can be deleted or inserted or substituted with another amino acid. Accordingly, the PYY₃₋₃₆ portions as present in a compound of formula (I) preferably include at least 29 amino acids of the native sequence of the PYY₃₋₃₆ portion. Preferably, the C-terminal six amino acids of native PYY₃₋₃₆ are all present in a molecule of the invention.

25 Typically conservative substitutions are the replacements, for one another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of Ser and Thr containing hydroxy residues, interchange of the acidic residues Asp and Glu, interchange between the amide residues Asn and Gln, interchange of the basic residues Lys and Arg, interchange of the aromatic residues Phe and Tyr, and interchange of the small-sized amino acids Ala, Ser,

30 Thr, Met and Gly. Guidance concerning how to make phenotypically silent amino acid substitutions, ie substitutions that do not alter the expressed phenotype, is provided in Bowie et al., *Science* 247:1306-1310, 1990.

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Table 3: Non-limiting examples of conservative amino acid substitutions

	Original Residue	Conservative Substitutions
5	Ala	Ser
	Arg	Lys
	Asn	Gln, His
	Asp	Glu
10	Cys	Ser
	Gln	Asn
	Glu	Asp
	His	Asn; Gln
	Ile	Leu, Val
15	Leu	Ile; Val
	Lys	Arg; Gln
	Met	Leu; Ile
	Phe	Met; Leu; Tyr
	Ser	Thr
20	Thr	Ser
	Trp	Tyr
	Tyr	Trp; Phe
	Val	Ile; Leu

- 25 Variants of the PYY₃₋₃₆ portion further include variants in which one or more amino acids (for example 2, 3 or 4) of the PYY₃₋₃₆ of one species are substituted by an amino acid present at the equivalent position in PYY derived from a different species. The sequences of PYYs of various species are included in Table 1 above. In particular, the PYY₃₋₃₆ portions of the molecule which comprise the human PYY sequence may be substituted by
- 30 one or more amino acids (for example 2, 3 or 4) which are present at the equivalent position in PYY derived from a different species.

Derivatives

- A compound of the invention may comprise the structure of formula (I) modified by well
- 35 known processes including amidation, glycosylation, carbamylation, acylation, for example acetylation, sulfation, phosphorylation, cyclization, lipidization and pegylation. The structure of formula (I) may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

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A compound of the invention may be a fusion protein, whereby the structure of formula (I) is fused to another protein or polypeptide (the fusion partner) using recombinant methods known in the art. Alternatively, such a fusion protein may be synthetically synthesized by any known method. Such a fusion protein comprises the structure of formula (I). Any suitable peptide or protein can be used as the fusion partner (e.g., serum albumin, carbonic anhydrase, glutathione-S-transferase or thioredoxin, etc.). Preferred fusion partners will not have an adverse biological activity *in vivo*. Such fusion proteins may be made by linking the carboxy-terminus of the fusion partner to the amino-terminus of the structure of formula (I) or vice versa. Optionally, a cleavable linker may be used to link the structure of formula (I) to the fusion partner. A resulting cleavable fusion protein may be cleaved *in vivo* such that an active form of a compound of the invention is released. Examples of such cleavable linkers include, but are not limited to, the linkers D-D-D-D-Y, G-P-R, A-G-G and H-P-F-H-L, which can be cleaved by enterokinase, thrombin, ubiquitin cleaving enzyme and renin, respectively. See, e.g., U.S. Patent No. 6,410,707.

A compound of the invention may be a physiologically functional derivative of the structure of formula (I). The term "physiologically functional derivative" is used herein to denote a chemical derivative of a compound of formula (I) having the same physiological function as the corresponding unmodified compound of formula (I). For example, a physiologically functionally derivative may be convertible in the body to a compound of formula (I). According to the present invention, examples of physiologically functional derivatives include esters, amides, and carbamates; preferably esters and amides.

Pharmaceutically acceptable esters and amides of the compounds of the invention may comprise a C₁₋₂₀ alkyl-, C₂₋₂₀ alkenyl-, C₅₋₁₀ aryl-, C₅₋₁₀ ar-C₁₋₂₀ alkyl-, or amino acid-ester or -amide attached at an appropriate site, for example at an acid group. Examples of suitable moieties are hydrophobic substituents with 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include, but are not limited to, the following: lauroyl (C₁₂H₂₃), palmityl (C₁₅H₃₁), oleyl (C₁₅H₂₉), stearyl (C₁₇H₃₅), cholate; and deoxycholate.

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Methods for lipidization of sulfhydryl-containing compounds with fatty acid derivatives are disclosed in U.S. Patent No. 5,936,092; U.S. Patent No. 6,093,692; and U.S. Patent No. 6,225,445. Fatty acid derivatives of a compound of the invention comprising a compound of the invention linked to fatty acid via a disulfide linkage may be used for delivery of a compound of the invention to neuronal cells and tissues. Lipidisation markedly increases the absorption of the compounds relative to the rate of absorption of the corresponding unlipidised compounds, as well as prolonging blood and tissue retention of the compounds. Moreover, the disulfide linkage in lipidised derivative is relatively labile in the cells and thus facilitates intracellular release of the molecule from the fatty acid moieties. Suitable lipid-containing moieties are hydrophobic substituents with 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include, but are not limited to, the following: palmityl ($C_{15}H_{31}$), oleyl ($C_{15}H_{29}$), stearyl ($C_{17}H_{35}$), cholate; and deoxycholate.

Cyclization methods include cyclization through the formation of a disulfide bridge and head-to-tail cyclization using a cyclization resin. Cyclized peptides may have enhanced stability, including increased resistance to enzymatic degradation, as a result of their conformational constraints. Cyclization may in particular be expedient where the uncyclized peptide includes an N-terminal cysteine group. Suitable cyclized peptides include monomeric and dimeric head-to-tail cyclized structures. Cyclized peptides may include one or more additional residues, especially an additional cysteine incorporated for the purpose of formation of a disulfide bond or a side chain incorporated for the purpose of resin-based cyclization.

A compound of the invention may be a pegylated structure of formula (I). Pegylated compounds of the invention may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337).

Chemical moieties for derivitization of a compound of the invention may also be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol

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copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. A polymer moiety for derivatisation of a compound of the invention may be of any molecular weight, and may be branched or unbranched. For ease in handling and manufacturing, the preferred molecular weight of a polyethylene glycol for derivatisation of a compound of the invention is from about 1 kDa to about 100 kDa, the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight. Polymers of other molecular weights may be used, depending on the desired therapeutic profile, for example the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog. For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

Salts and solvates of compounds of the invention that are suitable for use in a medicament are those wherein a counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the compounds of formula (I) and their pharmaceutically acceptable salts or solvates.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed with hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycollic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, and isethionic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical

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acceptable salts. Pharmaceutically acceptable salts with bases include ammonium salts, alkali metal salts, for example potassium and sodium salts, alkaline earth metal salts, for example calcium and magnesium salts, and salts with organic bases, for example dicyclohexylamine and N-methyl-D-glucamine.

5

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. Such complexes are known as "solvates". For example, a complex with water is known as a "hydrate". The present invention provides solvates of compounds of the invention.

10

Conditions:

The invention provides a pharmaceutical composition comprising a compound of formula (I). The invention further provides the compound of formula (I) for use as a medicament.

15

The invention also provides a compound of formula (I) for use in the treatment of obesity or diabetes. The invention further provides a compound of formula (I) for use in reduction of appetite in a subject, for use in reduction of food intake in a subject, or for use in reduction of calorie intake in a subject.

20

The invention further provides the use of a compound of formula (I) for the manufacture of a medicament for the treatment of obesity or diabetes. The invention also provides the use of a compound of formula (I) for the manufacture of a medicament for reducing appetite in a subject, reducing food intake in a subject, or reducing calorie intake in a subject.

25

The invention further provides a method of treating obesity or diabetes in a subject in need thereof comprising administering to the subject an effective amount of a compound of formula (I). The invention also provides a method of reducing appetite in a subject, reducing food intake in a subject, or reducing calorie intake in a subject, comprising administering to the subject an effective amount of a compound of formula (I).

30

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The subject to whom the compound is administered may be overweight, for example, obese. Alternatively, or in addition, the subject may be diabetic, for example having insulin resistance or glucose intolerance, or both. The subject may have diabetes mellitus, for example, the subject may have Type II diabetes. The subject may be overweight, for
5 example, obese and have diabetes mellitus, for example, Type II diabetes.

In addition, or alternatively, the subject may have, or may be at risk of having, a disorder in which obesity or being overweight is a risk factor. Such disorders include, but are not limited to, cardiovascular disease, for example hypertension, atherosclerosis, congestive
10 heart failure, and dyslipidemia; stroke; gallbladder disease; osteoarthritis; sleep apnea; reproductive disorders for example, polycystic ovarian syndrome; cancers, for example breast, prostate, colon, endometrial, kidney, and esophagus cancer; varicose veins; acanthosis nigricans; eczema; exercise intolerance; insulin resistance; hypertension hypercholesterolemia; cholelithiasis; osteoarthritis; orthopedic injury; insulin resistance, for
15 example, type 2 diabetes and syndrome X; and thromboembolic disease (see Kopelman, *Nature* 404:635-43; Rissanen et al., *British Med. J.* 301, 835, 1990).

Other disorders associated with obesity include depression, anxiety, panic attacks, migraine headaches, PMS, chronic pain states, fibromyalgia, insomnia, impulsivity,
20 obsessive compulsive disorder, and myoclonus. Furthermore, obesity is a recognized risk factor for increased incidence of complications of general anesthesia. (See e. g., Kopelman, *Nature* 404:635-43, 2000). In general, obesity reduces life span and carries a serious risk of co-morbidities such as those listed above.

25 Other diseases or disorders associated with obesity are birth defects, maternal obesity being associated with increased incidence of neural tube defects, carpal tunnel syndrome (CTS); chronic venous insufficiency (CVI); daytime sleepiness; deep vein thrombosis (DVT); end stage renal disease (ESRD); gout; heat disorders; impaired immune response; impaired respiratory function; infertility; liver disease; lower back pain; obstetric and
30 gynecologic complications; pancreatitis; as well as abdominal hernias; acanthosis nigricans; endocrine abnormalities; chronic hypoxia and hypercapnia; dermatological effects; elephantitis; gastroesophageal reflux; heel spurs; lower extremity edema;

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mammegaly which causes considerable problems such as bra strap pain, skin damage, cervical pain, chronic odors and infections in the skin folds under the breasts, etc.; large anterior abdominal wall masses, for example abdominal panniculitis with frequent panniculitis, impeding walking, causing frequent infections, odors, clothing difficulties,
5 low back pain; musculoskeletal disease; pseudo tumor cerebri (or benign intracranial hypertension), and sliding hiatal hernia.

The present invention further provides a method for increasing energy expenditure in a subject. The method includes, for example, peripherally administering a therapeutically
10 effective amount of a compound of the invention to the subject, thereby altering energy expenditure. Energy is burned in all physiological processes. The body can alter the rate of energy expenditure directly, by modulating the efficiency of those processes, or changing the number and nature of processes that are occurring. For example, during digestion the body expends energy moving food through the bowel, and digesting food,
15 and within cells, the efficiency of cellular metabolism can be altered to produce more or less heat.

In one aspect, the method of the invention involves manipulation of the arcuate circuitry, that alter food intake coordinately and reciprocally alter energy expenditure. Energy
20 expenditure is a result of cellular metabolism, protein synthesis, metabolic rate, and calorie utilization. Thus, in this aspect of the invention, administration of a compound of formula (I) results in increased energy expenditure, and decreased efficiency of calorie utilization.

The invention also provides a method for improving a lipid profile in a subject. The
25 invention also provides a method for alleviating a condition or disorder that can be alleviated by reducing nutrient availability.

Appetite can be measured by any means known to one of skill in the art. For example, decreased appetite can be assessed by a psychological assessment. For example,
30 administration of a compound of the invention results in a change in perceived hunger, satiety, and/or fullness. Hunger can be assessed by any means known to one of skill in the art. For example, hunger is assessed using psychological assays, such as by an assessment

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of hunger feelings and sensory perception using a questionnaire, such as, but not limited to, a Visual Analog Score (VAS) questionnaire. In one specific, non-limiting example, hunger is assessed by answering questions relating to desire for food, drink, prospective food consumption, nausea, and perceptions relating to smell or taste.

5

A compound of the invention may be used for weight control and treatment, for example reduction or prevention of obesity, in particular any one or more of the following:

preventing and reducing weight gain; inducing and promoting weight loss; and reducing

obesity as measured by the Body Mass Index. A compound of the invention may be used

10 in the control of any one or more of appetite, satiety and hunger, in particular any one or more of the following: reducing, suppressing and inhibiting appetite; inducing, increasing,

enhancing and promoting satiety and sensations of satiety; and reducing, inhibiting and

suppressing hunger and sensations of hunger. A compound of the invention may be used

in maintaining any one or more of a desired body weight, a desired Body Mass Index, a

15 desired appearance and good health.

A subject may be a subject who desires weight loss, for example female and male subjects who desire a change in their appearance. A subject may desire decreased feelings of

hunger, for example the subject may be a person involved in a lengthy task that requires a

20 high level of concentration, for example soldiers on active duty, air traffic controllers, or truck drivers on long distance routes, etc.

The present invention may also be used in treating, prevention, ameliorating or alleviating conditions or disorders caused by, complicated by, or aggravated by a relatively high

25 nutrient availability. The term "condition or disorder which can be alleviated by reducing caloric (or nutrient) availability" is used herein to denote any condition or disorder in a

subject that is either caused by, complicated by, or aggravated by a relatively high nutrient availability, or that can be alleviated by reducing nutrient availability, for example by

decreasing food intake. Subjects who are insulin resistant, glucose intolerant, or have any

30 form of diabetes mellitus, for example, type 1, 2 or gestational diabetes, can also benefit from methods in accordance with the present invention.

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Conditions or disorders associated with increased caloric intake include, but are not limited to, insulin resistance, glucose intolerance, obesity, diabetes, including type 2 diabetes, eating disorders, insulin-resistance syndromes, and Alzheimer's disease.

5 According to the present invention, a compound of formula (I) is preferably used in the treatment of a human. However, while the compounds of the invention will typically be used to treat human subjects they may also be used to treat similar or identical conditions in other vertebrates for example other primates; farm animals for example swine, cattle and poultry; sport animals for example horses; companion animals for example dogs and
10 cats.

Compositions

While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation or composition. Accordingly, the invention
15 provides a pharmaceutical formulation comprising a compound of formula (I), or a variant or derivative thereof, or a salt or solvate thereof, as defined above and a pharmaceutically acceptable excipient. Pharmaceutical compositions of the invention may take the form of a pharmaceutical formulation as described below.

20 The pharmaceutical formulations according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurized aerosols, nebulizers or insufflators), rectal and topical (including dermal, transdermal, transmucosal, buccal, sublingual, and
25 intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of
30 bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely

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divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as
5 discrete units such as capsules, cachets or tablets each containing a predetermined amount
of the active ingredient; as a powder or granules; as a solution or a suspension in an
aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-
oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or
paste. Various pharmaceutically acceptable carriers and their formulation are described in
10 standard formulation treatises, e.g., *Remington's Pharmaceutical Sciences* by E. W.
Martin. See also Wang, Y. J. and Hanson, M. A., *Journal of Parenteral Science and
Technology*, Technical Report No. 10, Supp. 42:2S, 1988.

A tablet may be made by compression or moulding, optionally with one or more accessory
15 ingredients. Compressed tablets may be prepared by compressing in a suitable machine
the active ingredient in a free-flowing form such as a powder or granules, optionally mixed
with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent.
Moulded tablets may be made by moulding in a suitable machine a mixture of the
powdered compound moistened with an inert liquid diluent. The tablets may optionally be
20 coated or scored and may be formulated so as to provide slow or controlled release of the
active ingredient therein. The present compounds can, for example, be administered in a
form suitable for immediate release or extended release. Immediate release or extended
release can be achieved by the use of suitable pharmaceutical compositions comprising the
present compounds, or, particularly in the case of extended release, by the use of devices
25 such as subcutaneous implants or osmotic pumps. The present compounds can also be
administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain,
for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate
30 as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or
flavoring agents such as those known in the art; and immediate release tablets which can
contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium

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stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula (I) can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used.

- 5 Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl
- 10 cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.
- 15 Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose
- 20 containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration
- 25 include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor. An aqueous carrier may be, for example, an isotonic
- 30 buffer solution at a pH of from about 3.0 to about 8.0, preferably at a pH of from about 3.5 to about 7.4, for example from 3.5 to 6.0, for example from 3.5 to about 5.0. Useful buffers include sodium citrate-citric acid and sodium phosphate-phosphoric acid, and

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sodium acetate/acetic acid buffers. The composition preferably does not include oxidizing agents and other compounds that are known to be deleterious to PYY and PYY agonists. Excipients that can be included are, for instance, other proteins, such as human serum albumin or plasma preparations. If desired, the pharmaceutical composition may also
5 contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in
10 saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art. Conveniently in compositions for nasal aerosol or inhalation administration the compound of the invention is delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer, with the use of a suitable
15 propellant, e.g., dichlorodifluoro-methane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator can be formulated to contain a powder mix of the compound and a suitable powder base,
20 for example lactose or starch. In one specific, non-limiting example, a compound of the invention is administered as an aerosol from a metered dose valve, through an aerosol adapter also known as an actuator. Optionally, a stabilizer is also included, and/or porous particles for deep lung delivery are included (e.g., see U.S. Patent No. 6,447,743).

25 Formulations for rectal administration may be presented as a retention enema or a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

30 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as

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gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

- 5 Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having
10 regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the invention are also suitably administered as sustained-release systems. Suitable examples of sustained-release systems of the invention include suitable
15 polymeric materials, for example semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules; suitable hydrophobic materials, for example as an emulsion in an acceptable oil; or ion exchange resins; and sparingly soluble derivatives of the compound of the invention, for example, a sparingly soluble salt. Sustained-release systems may be administered orally; rectally; parenterally; intracisternally; intravaginally;
20 intraperitoneally; topically, for example as a powder, ointment, gel, drop or transdermal patch; buccally; or as an oral or nasal spray.

Preparations for administration can be suitably formulated to give controlled release of compounds of the invention. For example, the pharmaceutical compositions may be in the
25 form of particles comprising one or more of biodegradable polymers, polysaccharide jellifying and/or bioadhesive polymers, amphiphilic polymers, agents capable of modifying the interface properties of the particles of the compound of formula (I). These compositions exhibit certain biocompatibility features which allow a controlled release of the active substance. See U.S. Patent No. 5,700,486.

30

A compound of the invention may be delivered by way of a pump (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201, 1987; Buchwald et al., *Surgery* 88:507, 1980;

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Saudek et al., *N. Engl. J. Med.* 321:574, 1989) or by a continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The key factor in selecting an appropriate dose is the result obtained, as measured by decreases in total body weight or ratio of fat to lean mass, or by other criteria for measuring control or prevention of obesity or prevention of obesity-related conditions, as are deemed appropriate by the practitioner. Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533, 1990). In another aspect of the disclosure, compounds of the invention are delivered by way of an implanted pump, described, for example, in U.S. Patent No. 6,436,091; U.S. Patent No. 5,939,380; U.S. Patent No. 5,993,414.

Implantable drug infusion devices are used to provide patients with a constant and long term dosage or infusion of a drug or any other therapeutic agent. Essentially such device may be categorized as either active or passive. A compound of the present invention may be formulated as a depot preparation. Such a long acting depot formulation can be administered by implantation, for example subcutaneously or intramuscularly; or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials, for example as an emulsion in an acceptable oil; or ion exchange resins; or as a sparingly soluble derivatives, for example, as a sparingly soluble salt.

A therapeutically effective amount of a compound of the invention may be administered as a single pulse dose, as a bolus dose, or as pulse doses administered over time. Thus, in pulse doses, a bolus administration of a compound of the invention is provided, followed by a time period wherein no a compound of the invention is administered to the subject, followed by a second bolus administration. In specific, non-limiting examples, pulse doses of a compound of the invention are administered during the course of a day, during the course of a week, or during the course of a month.

In one embodiment, a therapeutically effective amount of a compound of the invention is administered with a therapeutically effective amount of another agent, for example an additional appetite suppressant, a food-intake-reducing, plasma glucose-lowering or

-30-

plasma lipid-altering agent. Specific, non-limiting examples of an additional appetite suppressant include amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine, fenfluramine, dexfenfluramine, and fluoxetine. The compound of the invention can be administered simultaneously with the additional appetite suppressant, or it may be administered sequentially. Thus, in one embodiment, the compound of the invention is formulated and administered with an appetite suppressant as a single dose.

A compound of the invention may be administered whenever the effect, e.g., appetite suppression, decreased food intake, or decreased caloric intake, is desired, or slightly before to whenever the effect is desired, such as, but not limited to about 10 minutes, about 15 minutes, about 30 minutes, about 60 minutes, about 90 minutes, or about 120 minutes, before the time the effect is desired.

The therapeutically effective amount of a compound of the invention will be dependent on the molecule utilized, the subject being treated, the severity and type of the affliction, and the manner and route of administration. For example, a therapeutically effective amount of a compound of the invention may vary from about 0.01 μg per kilogram (kg) body weight to about 1 g per kg body weight, for example about 0.1 μg to about 20 mg per kg body weight, for example about 1 μg to about 5 mg per kg body weight, or about 5 μg to about 1 mg per kg body weight.

In one embodiment of the invention, a compound of the invention may be administered to a subject at from 5 to 1000 nmol per kg bodyweight, for example at from 10 to 750 nmol per kg bodyweight, for example at from 20 to 500 nmol per kg bodyweight, in particular at from 30 to 240 nmol per kg bodyweight. For a 75kg subject, such doses correspond to dosages of from 375 nmol to 75 μmol , for example from 750nmol to 56.25 μmol , for example from 1.5 to 37.5 μmol , in particular from 2.25 to 18 μmol .

In an alternative embodiment, a compound of the invention may be administered to a subject at 0.5 to 135 picomole (pmol) per kg body weight, for example 5 to 100 picomole (pmol) per kg body weight, for example 10 to 90 picomole (pmol) per kg body weight, for

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example about 72 pmol per kg body weight. In one specific, non-limiting example, a compound of the invention is administered in a dose of about 1 nmol or more, 2 nmol or more, or 5 nmol or more. In this example, the dose of the compound of the invention is generally not more than 100 nmol, for example, the dose is 90 nmols or less, 80 nmols or less, 70 nmols or less, 60 nmols or less, 50 nmols or less, 40 nmols or less, 30 nmols or less, 20 nmols or less, 10 nmols. For example, a dosage range may comprise any combination of any of the specified lower dose limits with any of the specified upper dose limits. Thus, examples of non-limiting dose ranges of compounds of the invention are within the range of from 1 to 100 nmols, from 2 to 90 mols, from 5 to 80 nmols.

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In one specific, non-limiting example, from about 1 to about 50 nmol of a compound of the invention is administered, for example about 2 to about 20 nmol, for example about 10 nmol is administered as a subcutaneous injection. The exact dose is readily determined by one of skill in the art based on the potency of the specific compound utilized, the route of delivery of the compound and the age, weight, sex and physiological condition of the subject.

15

Suitable doses of compounds of the invention also include those that result in a reduction in calorie intake, food intake, or appetite, or increase in energy expenditure that is equivalent to the reduction in calorie intake, food intake, or appetite, or to increase the energy expenditure, caused by the normal postprandial level of PYY3-36. Examples of doses include, but are not limited to doses that produce the effect demonstrated when the serum levels of PYY are from about 40 pM to about 60 pM, or from about 40 pM to about 45 pM, or about 43 pM.

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The disclosure is illustrated by the following non-limiting Examples.

8. EXAMPLES

30 Materials and Methods:

Male C57BL/6 mice (20-30g) were used for all mouse experiments. Mice were individually housed in IVC cages. Animals were randomised by weight and fasted

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overnight for 16hrs before intraperitoneal injection at 9am. Food intake was measured at 1, 2, 3, 4, 6, 8 and 24 hours post injection. All peptide solutions were prepared freshly the morning of the study and injected as 100ul. All statistics are calculated using a one-way ANOVA with Dunnett's post-test or one-way ANOVA with Bonferroni post-test.

5

Peptide Synthesis

Peptide synthesis of PYY₃₋₃₆Lys₁₂ and PYY₃₋₃₆Lys₁₂ lauryl was carried out on a tryptic amide linker resin. The sequences (except for position 12) were the human PYY sequences. Amino acids were attached using the Fmoc strategy. Each amino acid was added sequentially from the C- to the N-termini. Peptide couplings were mediated by the reagent TBTU. Peptide cleavage from the resin was achieved with trifluoroacetic acid in the presence of scavengers. Native PYY(3-36) is obtained as described previously (WO03/026591); *de novo* synthesis using tryptic amide resin and Fmoc chemistry is also possible.

15

Peptides were purified by reverse phase HPLC. Full quality control was performed on all purified peptides and peptides were shown to be greater than 95% pure by HPLC in two buffer systems. Amino acid analysis following acid hydrolysis confirmed the amino acid composition. MALDI-MS showed the expected molecular ion.

20

Results:

Example 1: Administration of 3 different PYY analogues to mice

The effects of PYY₃₋₃₆ (at 30nmol/kg) (SEQ ID NO:2), PYY₃₋₃₆Lys₁₂ (at two dosages – 60nmol/kg and 120nmol/kg) (SEQ ID NO:13), and PYY₃₋₃₆Lys₁₂Lauryl (at 120nmol/kg) (SEQ ID NO:14), were compared after a single injection. A control of saline was used.

25

The results are shown in the graph of Figure 1, in the time-interval bar charts of Figures 2 a) to 2 g) and in the comparative graph of Figure 3. In the figures, PYY₃₋₃₆Lys₁₂Lauryl is named PYY₃₋₃₆Lys₁₂Acyl. As is seen in the Figures, PYY₃₋₃₆Lys₁₂Lauryl had a similar decreasing effect on food intake as PYY₃₋₃₆ until 8 hours. As is seen particularly in the Figure 1 graph showing cumulative food intake, the effect of PYY₃₋₃₆ was lost after 8

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hours and by 24 hours, the cumulative food intake for the 24 hour period of mice given PYY₃₋₃₆ was essentially the same as those given the saline control. That is to say that the initial decrease in food intake was compensated for by an increase in food intake between 8 and 24 hours. On the other hand, the cumulative food intake for the mice given PYY₃₋₃₆Lys₁₂Lauryl remained below the saline control, with an overall reduction in food intake of 6.1%. The PYY₃₋₃₆Lys₁₂ compound had essentially the same effect as the saline.

PYY₃₋₃₆Lys₁₂Lauryl (at 120 nmol/kg) is seen to have the most sustained effect when compared with saline control, PYY₃₋₃₆ (at 30nmol/kg) and PYY₃₋₃₆Lys₁₂ (at two dosages – 60nmol/kg and 120nmol/kg).

Example 2: Dose response experiment for PYY₃₋₃₆Lys₁₂Lauryl in mice

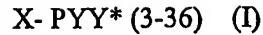
The effects of PYY₃₋₃₆Lys₁₂Lauryl (at three dosages – 60nmol/kg, 120nmol/kg and 240nmol/kg) were compared with PYY₃₋₃₆ (at 30nmol/kg) after a single injection. A control of saline was used.

The results are shown in the time-interval bar charts of Figures 4 a) to 4 g) and in the comparative graph of Figure 5. The results at the 1 hour, 2 hour and 3 hour time point (ie the amounts of food consumed in the first hour, the second hour and the third hour) show a dose-response relationship, with 240nmol/kg PYY₃₋₃₆Lys₁₂Lauryl achieving a greater effect than 120nmol/kg, and both showing a greater effect than 60nmol/kg. At all doses, the effects of PYY₃₋₃₆ and PYY₃₋₃₆Lys₁₂Lauryl wears off after a time and, as seen in Figure 5, eventually the food intake becomes greater (in a given time period) in the mice that had received the PYY₃₋₃₆ and PYY₃₋₃₆Lys₁₂Lauryl than in the saline control mice. The time at which that occurs is later for the PYY₃₋₃₆Lys₁₂Lauryl-treated mice (around 6 hours) than for the PYY₃₋₃₆-treated mice (around 4 hours) as seen in Figure 5.

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CLAIMS

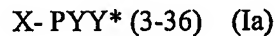
1. A compound of formula (I):



- 5 Wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile;
 PYY*(3-36) representing PYY (3-36) in which one or more residues is replaced by an
 acylated lysine group, the acyl group being selected from: CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀
 alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl;
 a variant or derivative thereof; or a salt or solvate thereof.

10

2. A compound as claimed in claim 1 which is a compound of formula (Ia):



PYY (3-36) being:

3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ile	Lys	Pro	Glu	Ala	Pro	Gly	Glu	Asp	Ala	Ser	Pro	Glu	Glu	Leu

15

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Asn	Arg	Tyr	Tyr	Ala	Ser	Leu	Arg	His	Tyr	Leu	Asn	Leu	Val	Thr

33	34	35	36
Arg	Gln	Arg	Tyr

SEQ ID NO:2

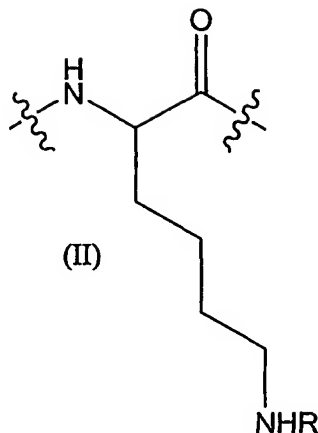
wherein X is selected from H, PYY₁₋₂ (ie Tyr Pro) and D-Allo-Ile;

20 PYY*(3-36) representing PYY (3-36) in which one or more of residues:

3 - Ile	7 - Ala
9 - Gly	12 - Ala
17 - Leu	22 - Ala
24 - Leu	28 - Leu

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is replaced by a residue (II):



- wherein R is selected from CO-C₁₋₂₀ alkyl, CO-C₂₋₂₀ alkenyl, CO-C₅₋₁₀ aryl and CO-C₅₋₁₀ ar-C₁₋₂₀ alkyl;
 5 a variant or derivative thereof; or a salt or solvate thereof.
3. A compound as claimed in claim 1 or claim 2 wherein the PYY*₃₋₃₆ is human PYY*₃₋₃₆.
 - 10 4. A compound as claimed in any one of claims 1 to 3 in which the PYY₃₋₃₆ is a variant of native PYY₃₋₃₆ with 1, 2, 3 or 4 modifications selected from deletions, insertions, inversions, repeats and substitutions.
 5. A compound as claimed in any one of claims 1 to 4 in which the PYY₃₋₃₆ includes at
 15 least 30 amino acids of the native human PYY₃₋₃₆ sequences.
 6. A compound as claimed in any one of claims 1 to 4 which is PYY₃₋₃₆ Lys₁₂-Acyl.
 7. A compound as claimed in any one of claims 1 to 6 which is a derivative that is
 20 modified by one or more processes selected from amidation, glycosylation, carbamylation, sulfation, phosphorylation, cyclization, lipidization and pegylation.
 8. A compound as claimed in any one of claims 1 to 7 which is a derivative that is a fusion protein.

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9. A compound as claimed in any one of claims 1 to 8 for use as a medicament.
10. A pharmaceutical composition comprising a compound as claimed in any one of
5 claims 1 to 9.
11. A compound as claimed in any one of claims 1 to 9 for use in the treatment of obesity or diabetes.
- 10 12. A compound as claimed in any one of claims 1 to 9 for use in the reduction of appetite in a subject, use in the reduction of food intake in a subject, or for use in the reduction of calorie intake in a subject.
- 15 13. A method of treating obesity or diabetes in a subject in need thereof comprising administering to the subject a compound of any one of claims 1 to 9.
14. A method of reducing appetite in a subject, reducing food intake in a subject, or reducing calorie intake in a subject, comprising administering to the subject a compound of any one of claims 1 to 9.
20
15. The method of claim 13 or claim 14, wherein the subject is overweight.
16. The method of claim 13 or claim 14, wherein the subject is obese.
- 25 17. The method of claim 13 or claim 14, wherein the subject is diabetic.
18. The method of any one of claims 13 to 17, wherein the compound is administered peripherally.
- 30 19. The method of any one of claims 13 to 17 wherein the compound is administered subcutaneously, intravenously, intramuscularly, intranasally, transdermally or sublingually.

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20. Use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment of obesity or diabetes.
- 5 21. Use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the reduction of appetite in a subject, for the reduction of food intake in a subject, or for the reduction of calorie intake in a subject.

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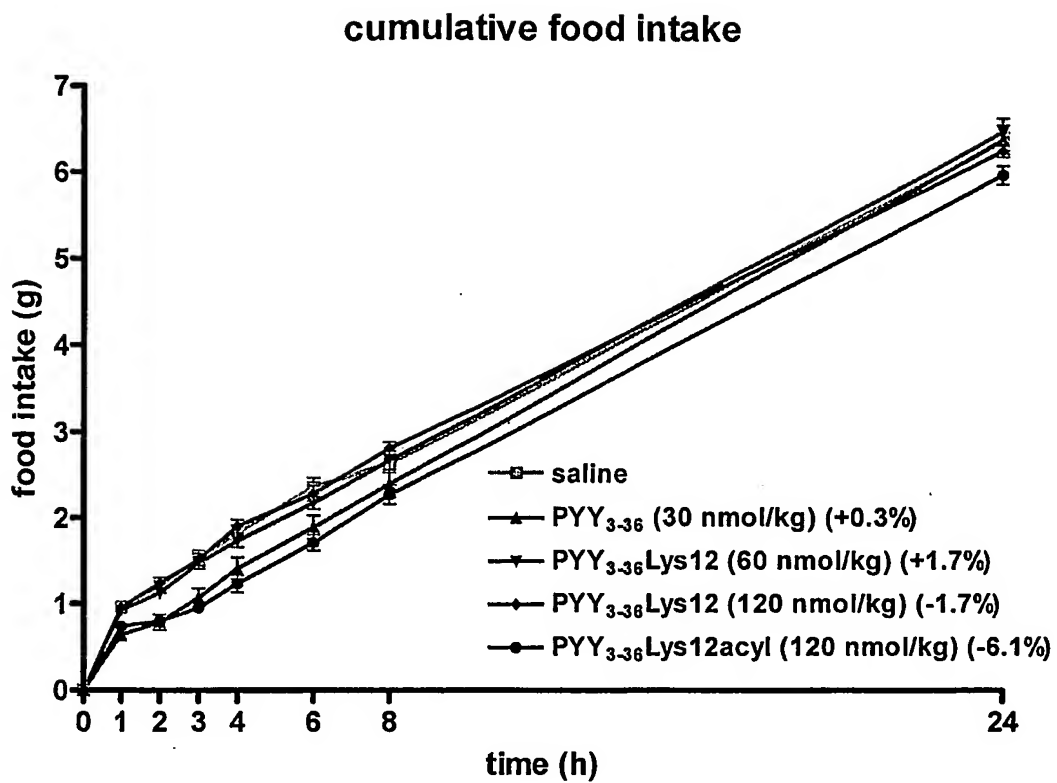


Figure 1

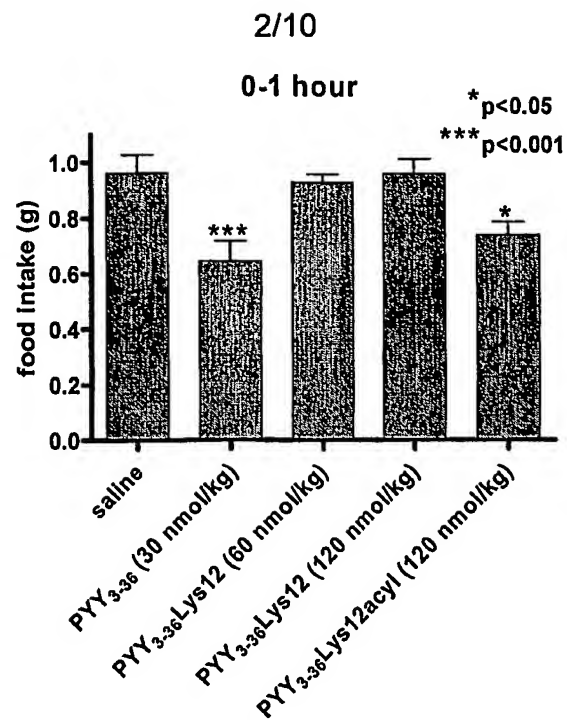


Figure 2 a)

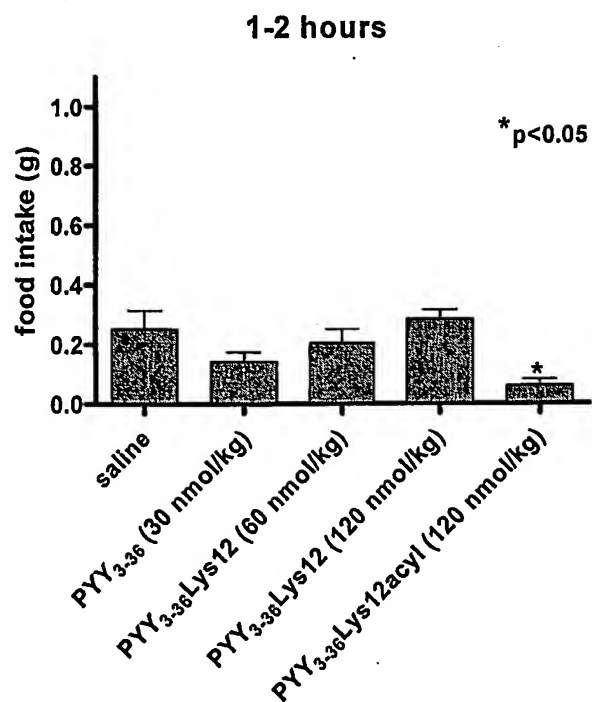


Figure 2 b)

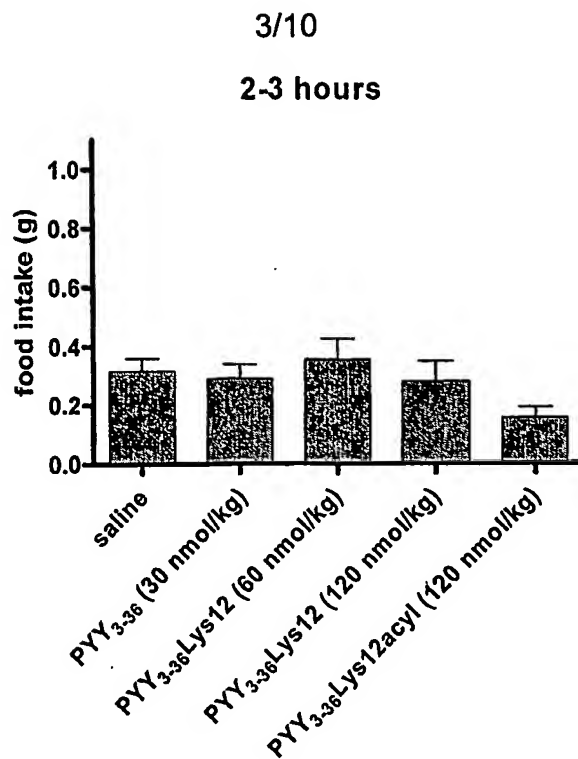


Figure 2 c)

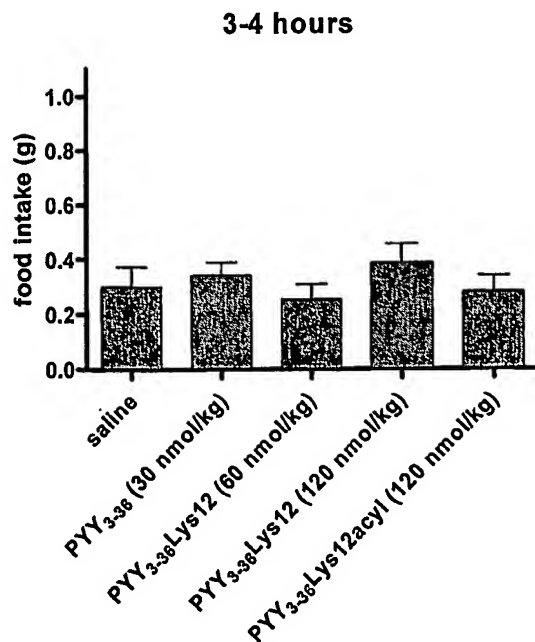


Figure 2 d)

4/10

4-6 hours

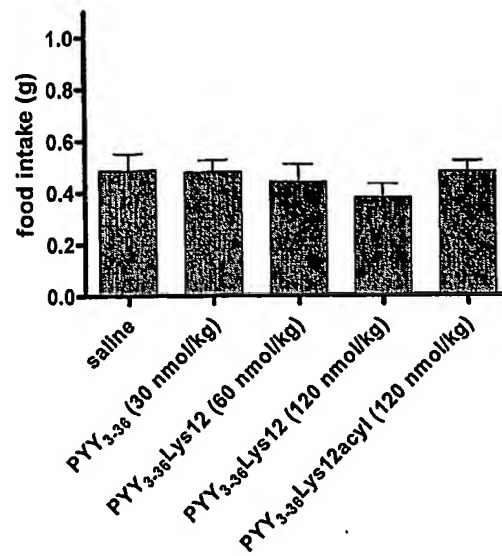


Figure 2 e)

6-8 hours

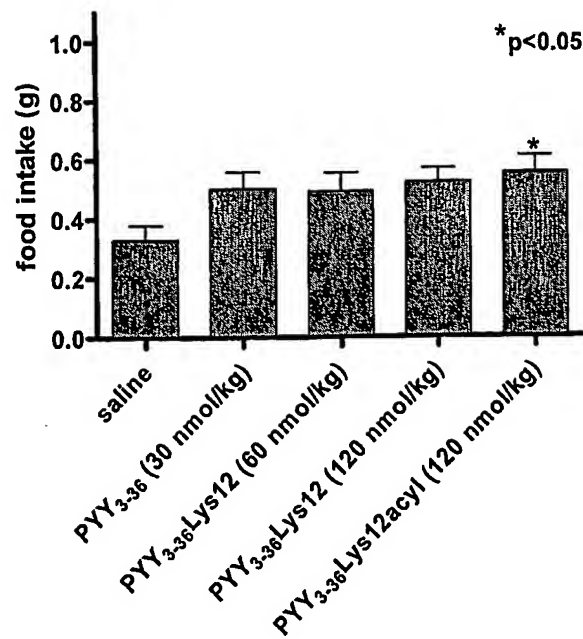


Figure 2 f)

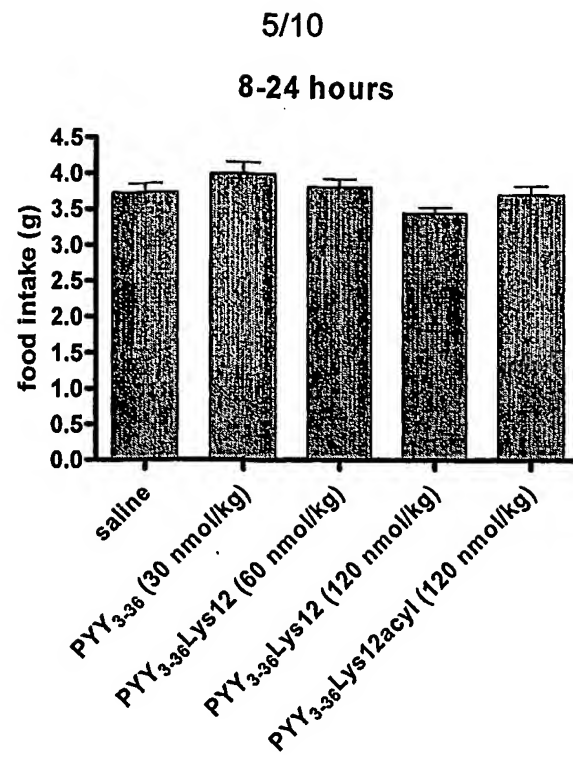


Figure 2 g)

6/10

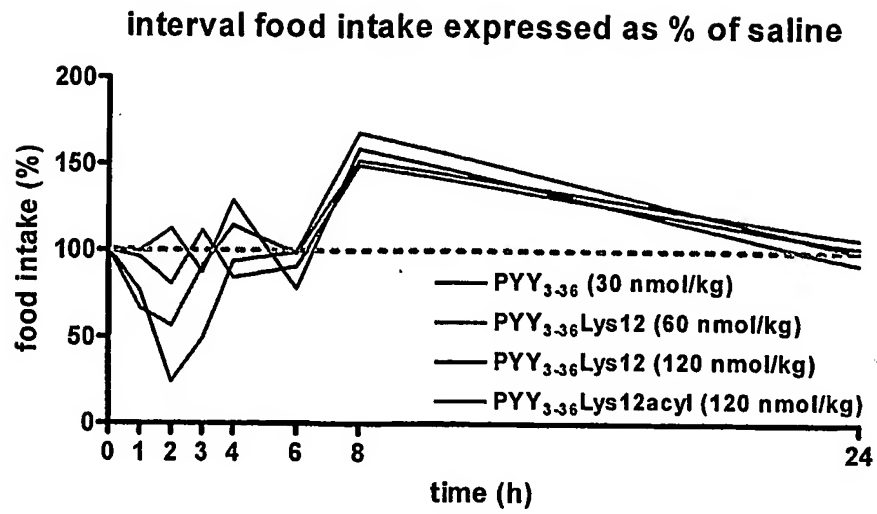


Figure 3

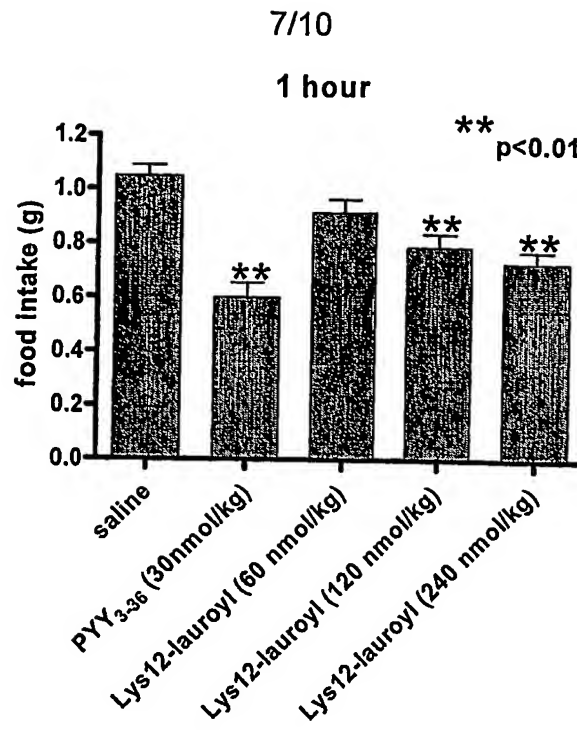


Figure 4 a)

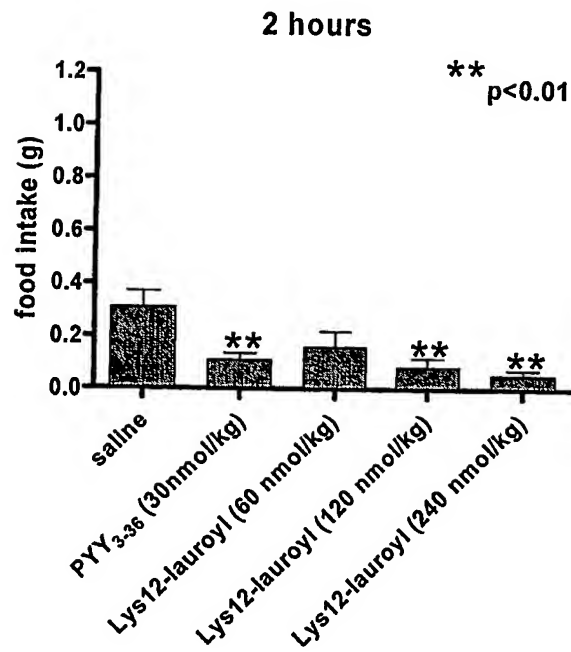


Figure 4 b)

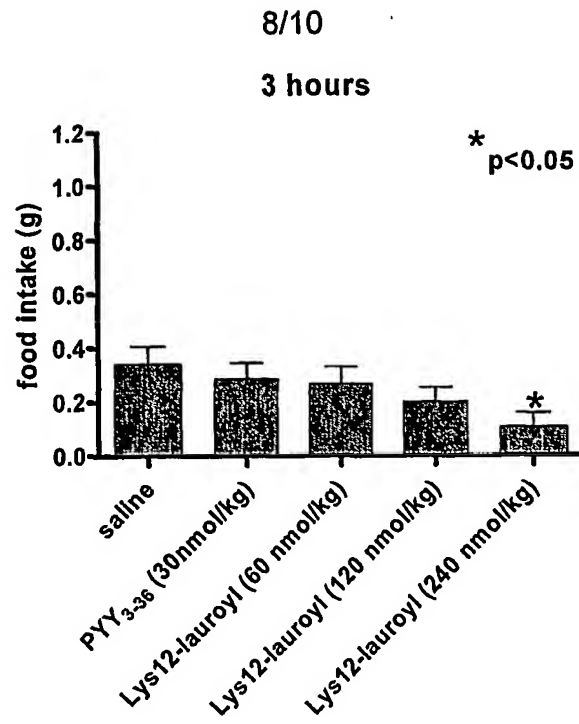


Figure 4 c)

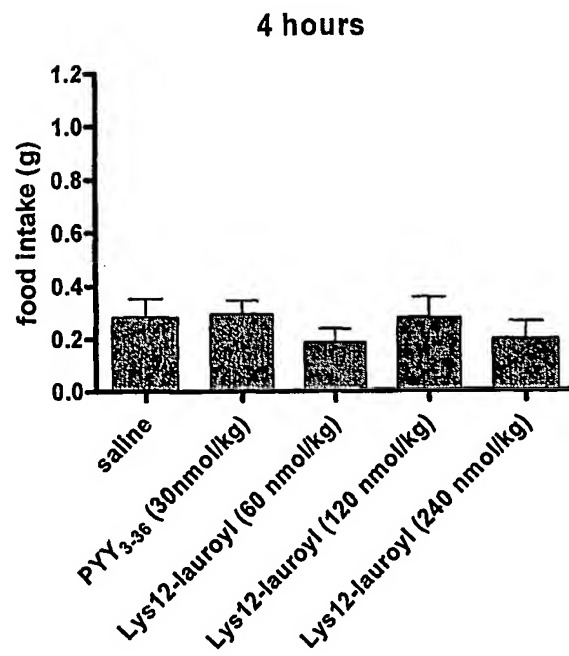


Figure 4 d)

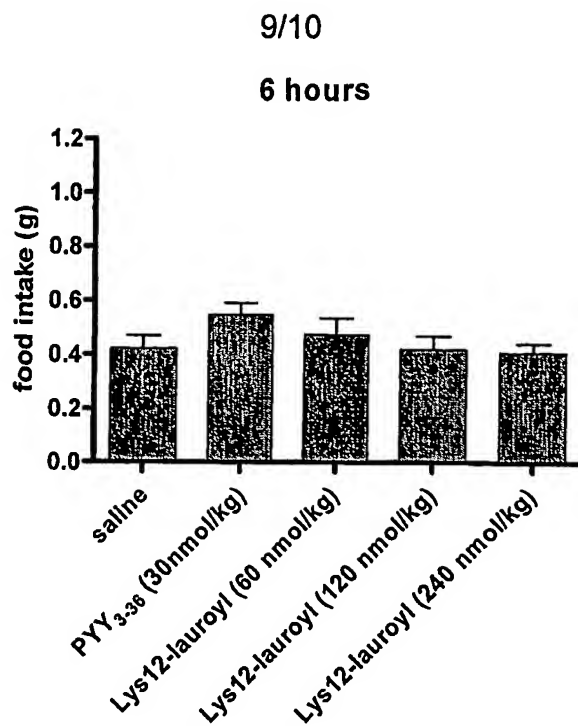


Figure 4 e)

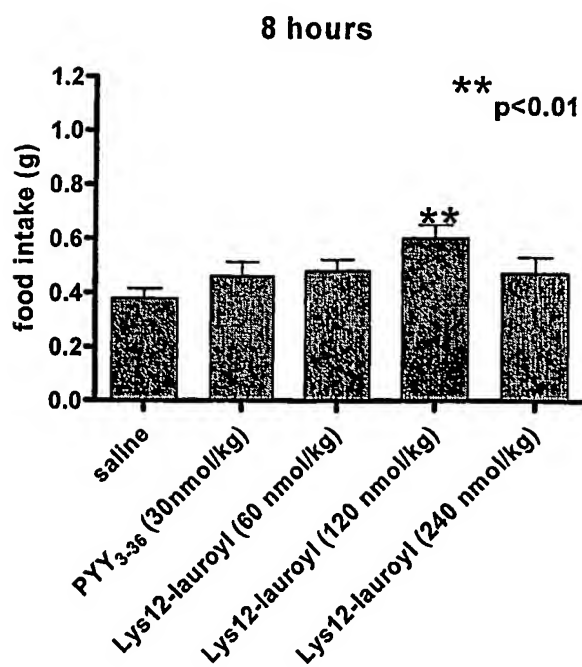


Figure 4 f)

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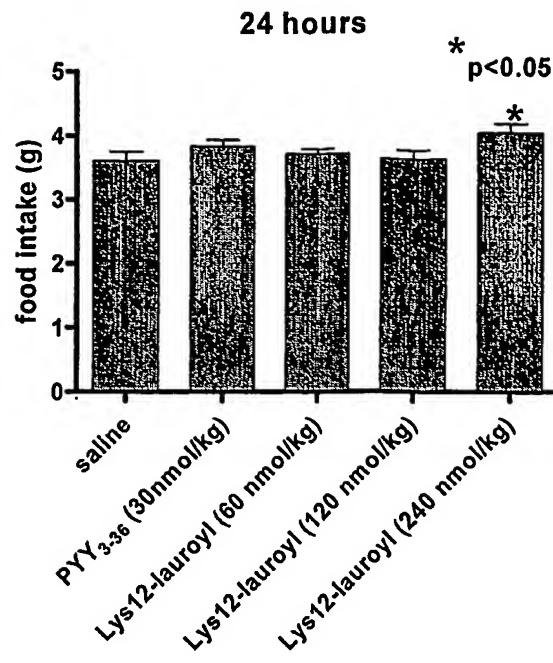


Figure 4 g)

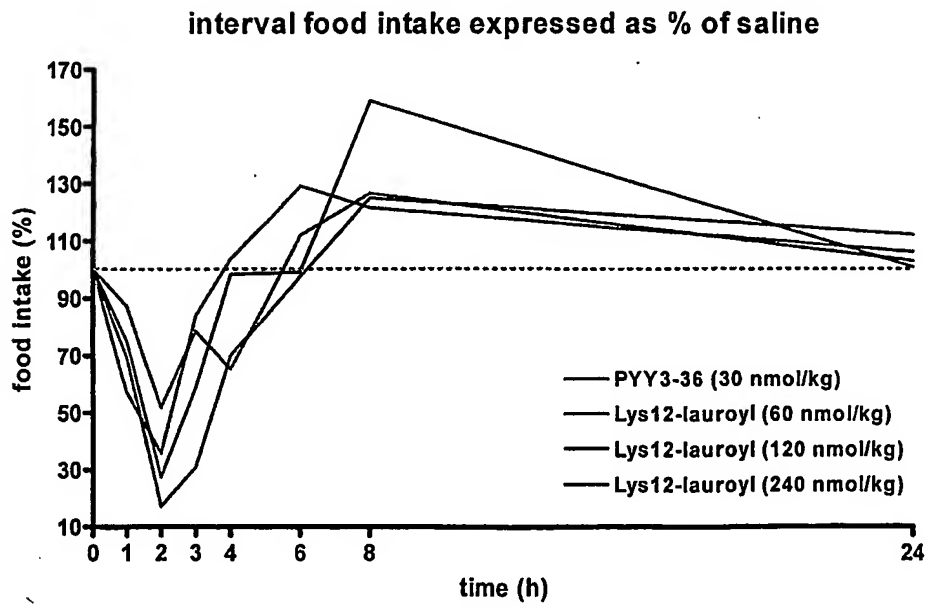


Figure 5

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/002473

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/176643 A1 (BRIDON DOMINIQUE P [US] ET AL) 11 August 2005 (2005-08-11) column 3, paragraph 73 - paragraph 75 the whole document	1-21
X	EP 0 708 179 A (LILLY CO ELI [US]) 24 April 1996 (1996-04-24) the whole document claim 1	1-21
X	WO 03/026591 A (IMP COLLEGE INNOVATIONS LTD [GB]; OREGON HEALTH AND SCIENCE UNIV [US];) 3 April 2003 (2003-04-03) page 65, line 3 - line 4	1-21

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-/-

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

19 September 2007

Date of mailing of the international search report

19/10/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

Petri, Bernhard

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/002473

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEGER R ET AL: "IDENTIFICATION OF CJC-1131-ALBUMIN BIOCONJUGATE AS A STABLE AND BIOACTIVE GLP-1/7-36) ANALOG" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, 6 September 2004 (2004-09-06), pages 4395-4398, XP008076568 ISSN: 0960-894X the whole document page 4395, left-hand column, paragraph 2 -----	1-21
X	US 6 268 343 B1 (KNUDSEN LISELOTTE BJERRE [DK] ET AL) 31 July 2001 (2001-07-31) the whole document claim 1 -----	1-21
P,X	WO 2006/095166 A (IMP INNOVATIONS LTD [GB]; MOORE STANLEY [GB]; GHATEI MOHAMMAD [GB]; BL) 14 September 2006 (2006-09-14) page 13, line 16 - page 14, line 12; examples 1-3 -----	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/002473

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/002473

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2005176643	A1	11-08-2005	NONE	
EP 0708179	A	24-04-1996	AT 285473 T	15-01-2005
			AU 3432295 A	02-05-1996
			BR 9504452 A	20-05-1997
			CA 2160753 A1	19-04-1996
			CN 1129224 A	21-08-1996
			CZ 9502666 A3	15-05-1996
			DE 69533868 D1	27-01-2005
			DE 69533868 T2	01-12-2005
			ES 2232820 T3	01-06-2005
			FI 954941 A	19-04-1996
			HU 73413 A2	29-07-1996
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			CA 2461345 A1	03-04-2003
			CN 1596119 A	16-03-2005
			EP 1499277 A2	26-01-2005
			JP 2005508324 T	31-03-2005
			MX PA04002751 A	08-09-2005
US 6268343	B1	31-07-2001	NONE	
WO 2006095166	A	14-09-2006	NONE	